crucial in order to suspend the mass of solid crystals emerging at the point of contact, which has been the common practical problem in traditional stirred tank crystallisers. The combination of the enhanced mixing that suspends crystal particles along the COBC and the plug flow characteristics that move the generated crystals downstream from the meeting point gives the best of both worlds. As antisolvent crystallisation is normally carried out isothermally, this becomes a relatively simple operation. Some experimental and modelling work on antisolvent crystallisation are in the public domain in COBC[169–171] and other devices.[172] Successful development and control of an antisolvent crystallisation for the production of a pharma API was reported where online FBRM and ATR-IR data were used to control concentration and maintain relative supersaturation.[173] At the time of composing this chapter, a 3 day continuous campaign of antisolvent crystallisation in COBC has been successfully performed.[174]

There are few industrial processes that require both antisolvent and cooling crystallisation steps with essentially two purposes. The first is to separate nucleation from growth as we discussed in the previous section. The second is to rely on antisolvent crystallisation to generate small crystals or crystal agglomerates, then to employ a cooling crystallisation step to either grow crystals or maintain these agglomerates for better filtration.

3.5.2.2 Seed Generator

Seed generation is notoriously time and energy consuming. Generally, the smaller the size and the larger the surface areas, the better the seed production with less seeds needing to be used. Traditionally this is done by either wet or dry milling. The former method entails smashing a solution containing crystals using a high shear stirrer, *e.g.* Silverson homogeniser, in either batch or flow set up. The batch set up resembles a kitchen smoothie machine and foams are often formed when air is entrained into the solution when operating at high rotational speeds; as the majority of the crystals are migrating into the foams, this defeats the purpose of milling. Antifoam agent can be used to alleviate this phenomenon, but the removal of this antifoam brings about more problems. The flow set up necessitates pumping and recycling the solution containing crystals from a tank through a rotor-stator type of high shearing device,[175] or using a turbulent jet.[66] Seeds generated this way often undergo agglomeration, but an ultrasonic device can be used to control and reduce this effect, although lengthening the process.[16]

Dry milling literally involves a 'pestle and mortar' type of device to grind crystals, either manually or by machine. This breaks up crystals and the required crystal sizes are obtained by sieving. The grinding process is repeated for oversize crystals, while the fines so generated are waste with hazards. It can often take weeks in order to achieve seed loading for one batch operation. This is not only energy intensive, but also un-scalable.